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IN THE MATTER OF
US Patent Application No. 09/380,327
by ROBERTSON et al.

Declaration under U.S.C.§ Rule 132

STATUTORY DECLARATION

I, David Alexander Clark of 444 Smith Ave., Burlington in the Province of Ontario, Canada, do solemnly and sincerely declare as follows:

1. I am the same David Alexander Clark who made a statutory declaration dated 16 December 2002 in respect of this matter.

2. I have been provided with copies of the following documents:

Abstract by Tremellen K.P. and Robertson S.A. entitled "Potential role for transforming growth factor beta in modulating the maternal immune response during early murine pregnancy" published by The Australian Society for Medical Research on 24-27 November 1996; and
Abstract by Tremellen K.P. and Robertson S.A. entitled "Isolation of seminal vesicle proteins responsible for the initiation of the post-mating inflammatory response" published by The Australian Society for Medical Research on 31 May 1996.

Copies of these two abstracts are annexed hereto as Exhibit DC-1.

3. I have been informed that both of these abstracts were published before the priority date of the present application, 6 March 1997, and have only recently come to the attention of the licensee of the present application, who is responsible for instructions in relation to this case.

4. I have also been provided with a copy of the paper by Robertson et al., "Role of high molecular weight seminal vesicle proteins in eliciting the uterine inflammatory response to semen in mice" (J Reproduction and Fertility (1996) 107, 265-277), and the abstract of a paper by Robertson and Seamark entitled "Granulocyte macrophage colony stimulating factor (GM-CSF) in the murine reproductive tract: stimulation by seminal factors" (Reprod Fertil Dev, (1990) 2(4): 359-68). The paper by Robertson et al is referred to in the specification at page 4 lines 18 to 22, and is reference 10 listed at page 30 of the specification. The paper by Robertson and Seamark is reference 8 cited at page 4 line 21 of the specification, and is reference 8 in the list at page 30. Copies of these documents are annexed hereto as Exhibits DC-2 and DC-3.

5. I am aware that it was known before the priority date that human seminal fluid contains high levels of TGFβ. This is disclosed in the paper by Nocera and Chu (1995) (Am. J. Reprod. Immunol. 33, 282-291), which is also referred to in the specification and is reference 22 in the list at page 30.

6. I have read and understood the two abstracts, and I do not consider that they convey any significant further information over and above the disclosures of the reference which are discussed at page 4 lines 14 to 29 of the specification.

7. Nor do I consider that they provide any significant information over and above any of the references previously cited by the Examiner, and which have been discussed in my earlier declarations in this matter.

8. I do not consider that either of these abstracts would lead a person of ordinary skill in the art as at the priority date, 6 March 1997, to consider that treatment with TGFβ would be useful in the treatment of an infertility condition as defined in the specification, including recurrent miscarriage or spontaneous abortion. The abstracts show that TGFβ elicited a non-specific inflammatory response. At the priority date inflammation was regarded as having an *anti*-fertility effect. For example, intrauterine devices were reported to exert a contraceptive effect by eliciting

intrauterine inflammation. In the condition called endometriosis, release of increased levels of proinflammatory cytokines such as TNF-α and interferon-γ was regarded as *preventing* spermatozoa from fertilizing oocytes, preventing the normal division of the fertilized ovum, and preventing normal outgrowth of the embryonic trophoblast cells which is required for attachment of the fertilized ovum to and invasion of the endometrium. Similarly, stimulation of release of proinflammatory cytokines by bacterial lipopolysaccharide (endotoxin) was a well-known cause of abortions.

9. I consider that the two abstracts and the earlier publications of Robertson et al and Robertson and Seamark would have led the person skilled in the art to consider that TGFβ would have an anti-fertility effect, and would cause rather than prevent abortion.

10. I note that the May abstract refers to a primary role for seminal TGFβ1 in initiating the post-mating inflammatory response in mice, while the November abstract refers to "investigation of the potential role of this response in generating a tolerogenic maternal immune response conducive to growth and survival and the semi-allogenic (sic) embryo during pregnancy." In the 1996 paper by Robertson et al (reference 10 in the specification) it was not clear how a proinflammatory stimulus, which was subsequently identified in the abstract as TGFβ, could promote development of immunological tolerance. At lines 10 to 11 of the introduction to that paper, the authors suggest that the hormone progesterone, not the proinflammatory stimulus, was responsible for causing a switch to a tolerogenic state. At the priority date, even though it was known that TGFβ had immunosuppressive properties, as well as many other biological properties, because the effects of plasma TGFβ had been shown in the abstracts to be proinflammatory, they would not be suspected of inducing a tolerance response.

11. Furthermore, the meaning of the expression "a tolerogenic maternal immune response conducive to the growth and survival of the semi-allogeneic embryo during pregnancy" is far from clear. The state of tolerance is a grossly observable phenomenon which may arise via one or more distinct underlying mechanisms. To add to the conceptual confusion prevailing in 1997, some investigators had been proposing that an active immune response, even immunostimulation, was required for successful pregnancy, and in the light of these proposals immunosuppression and

"tolerance", meaning absence of an immune response, would not clearly lead to enhanced success of pregnancy.

12. I therefore consider that a considerable amount of further work would have been required before any possible therapeutic application on the basis of the observations described in the abstracts could have been suggested. Consequently I consider that the two abstracts teach away from the claimed invention, and at most constitute an invitation for further experimentation.

I declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by prison or fine or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of any application or patent thereon.

DECLARED at Burlington this 9th day of September, 2003

David A. Clark

David A. Clark

Before me:

FULVIO DELIBATO
SOLICITOR
& NOTARY PUBLIC,

A person empowered to witness Statutory Declarations under the laws of the Province of Ontario, Canada.